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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/562,128	12/23/2005	Susumu Watanuki	Q92303	5572

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2100 PENNSYLVANIA AVE. NW
WASHINGTON, DC 20037-3213

EXAMINER	
GALLIS, DAVID E	

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07/10/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/562,128	WATANUKI ET AL.	
	Examiner	Art Unit	
	David E. Gallis	1609	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *3-6,13 and 18-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,7-12 and 14-17* is/are rejected.

7)☒ Claim(s) *1,2,7-11,12,14* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/27/06 and 5/15/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

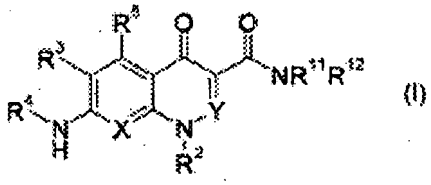
DETAILED ACTION

1. Claims 1 through 21 are pending. Claims 3 through 6, 13, and 18 through 21 have been withdrawn. This application is a National Stage of PCT/JP04/ 10781 filed July 22, 2004. Applicant has perfected the priority date of July 24, 2003.

Election/Restrictions

2. Applicant's election without traverse of Group IV is acknowledged by the examiner. The elected subject matter for Group IV is as follows:

Group IV, claims 1, 2, and 7 through 17, drawn to a quinolone derivative and pharmaceutical composition comprising a quinolone derivative, or a pharmaceutically acceptable salt thereof, represented by formulas (I) of claim 1 and (I-a) of claim 7 defined to contain the following specific functional groups:



(I)

$X=C\text{-}R^7$ (where R^7=H), $Y=C\text{-}R^6$ (where R^6=H), R^2=lower alkyl, R^3=halogen, R^4=cyclohexyl, R^5=hydrogen, R^{11}=hydrogen, R^{12}= lower alkyl substituted with $-CO_2H$.

3. Claim 13 which is drawn to an $NR^{11}R^{12}$ group forming a cyclic amino group has been withdrawn from consideration since it does not contain elected Group IV subject matter.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1, 2, 7 through 12, and 14 through 17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for P2Y12 and platlet

aggregation inhibition activity for a select compound of the elected subject matter, does not reasonably provide enablement for P2Y12 and platelet aggregation inhibition for all elected compounds and pharmaceutical compositions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

6. With respect to claims 1, 2, 7 through 12, and 14 through 17, Table 1 of the specification provides the results for the human platelet aggregation inhibition tests for 8 quinolone derivatives tested. None of the derivatives tested comprise the elected subject matter with regard to formula (I) structure. The only compounds enabled for platelet aggregation inhibition activity include phosphonic acid derivatives, a thioquinone derivative, a substituted pyrrolidinyl derivative, and a derivative with a fused piperidine ring structure. Table 2 of the specification provides the results for the inhibition activity for P2Y12 binding tests for 18 quinolone derivatives tested. A single derivative tested (*2-({[7-(cyclohexylamino)-1-(1-ethylpropyl)-6-fluoro-4-oxo-1,4-dihydrquinolin-3-yl)carbonyl}amino)-2-methylpropionic acid, example 28*) comprised the elected subject matter with regard to formula (I) structure. However, a survey of the literature suggests that P2Y12 inhibition is the critical feature of platelet aggregation inhibitors. Therefore, platelet aggregation inhibition is assume viable only for Example 28 and examples of closely related structures within the elected subject matter. These compounds are characterized as follows:

X=C-R^7 (where R^7=H), Y=C-R^6 (where R^6=H), R^2=straight or branched chain alkyl, R^3=halogen, R^4=cyclohexyl, R^5=hydrogen, R^{11}=hydrogen, R^{12}= straight or branched chain alkyl mono-substituted with $-CO_2H$.

This structure comprises the following enabled compounds according to formula (I) and (1-a): Disclosure Examples 28, 161, 162, 163, 165, 254, 255, 256, 269, 273, 274, 276, 277, 278, 280, 291, 292, 293, 493, 495, 506, 507, 510, 511, 525, 526, and 599.

"The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art, and the breadth of the claims", In re Rainer, 146 USPQ 218 (1965); In re Colianni, 195 USPQ 150, Ex parte Formal, 230 USPQ 546. 1) Since none of the elected compounds of formula (I) have associated inhibition data for platelet aggregation, the testing that would be required would be substantial. 2) The amount of guidance and direction presented in the disclosure is minimal. Specifics of the factors used in the calculated percent inhibition are not discussed in terms of 100% and 0% limits. 3) To reiterate, none of the elected compounds of formula (I) have associated inhibition data for platelet aggregation. Therefore there is a clear lack of working examples. 4) The nature of the invention is known for other active compounds, however, none with the analogous structures to those instantly claimed and elected. 5) The state of the prior art teaches related quinolones in bacteriological and antimicrobial applications, but not typically as platelet aggregation inhibitors, and therefore, 6) one skilled in art of clinical and research hematology would be needed to practice the invention. 7) Since there is little to no data available regarding the application of this class of compound to platelet aggregation, there is nothing to suggest any reasonable degree of predictability between structure and activity as a platelet aggregation inhibitor

or a P2Y12 inhibitor. In fact, Losasso et al. (J. Chemother. Oct. 1995, 7(5), 420-423), teaches that the platelet aggregation inhibiting ability of two related quinolones is only operable outside a clinically achievable concentration, if at all. In their work with two quinolone antimicrobial agents (lomefloxacin and sparfloxacin), Losasso et al state "When compared with saline, lomefloxacin and sparfloxacin, in the *in vitro* studies, did not inhibit ADP and collagen-induced platelet aggregation." (see page 421, RESULTS, ¶1) 8) The claims are broad and encompass not only platelet aggregation inhibition but also P2Y12 inhibition.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> **The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.**

8. Claims 12, and 15 through 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

9. Claim 12 is drawn to R^{12} as lower alkyl "respectively" substituted with one or more groups selected from option Group Q. The respective assignment of the lower alkyl R^{12} is unclear. A proviso reads that "at least one is substituted with a group of the Group P". As written, it is not clear if the substituent from Group Q must be substituted with a substituent from Group P, or if one substituent must come from Group P if more than one substituent is selected.

10. Claim 15 recites the limitation "The pharmaceutical composition". There is insufficient antecedent basis for this limitation in the claim, since none of the claims from which it depends recite a pharmaceutical composition.

11. Claims 15 through 17 recite the limitation "according to any one of claims 7 through 14". There is insufficient antecedent basis for this limitation in the claim since claim 13 has been withdrawn from consideration.

Claim Objections

12. Claims 1, 2, 7, 8, 9, 11, 12, and 14 are objected to because of the following informalities: These claims contain subject matter outside the elected Group IV subject matter as detailed above on page two of this Action. Appropriate correction is required.

13. Claims 8, 9, and 11 are objected to under 37 CFR 1.75 as being substantial duplicates of claim 7. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Claims 8, 9, and 11 are compound claims that encompass the same products that are encompassed by formula (I-a) of claim 7 as restricted to the elected Group IV subject matter.

14. Claim 10 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 10 recites the

limitation for R^4 as cycloalkyl where R^4 is already limited to cyclohexyl by formula (I-a) of claim 7 as restricted to the elected Group IV subject matter.

Allowable Subject Matter

15. Subject matter is allowable with regard to compounds of, and pharmaceutical compositions comprising, instant formula (I) and (I-a) wherein:

X=C-R^7 (where R^7=H), Y=C-R^6 (where R^6=H), R^2=straight or branched chain alkyl, R^3=halogen, R^4=cyclohexyl, R^5=hydrogen, R^{11}=hydrogen, R^{12}= straight or branched chain alkyl mono-substituted with $-CO_2H$.

This structure comprises the following enabled compounds according to formula (I) and (1-a): Disclosure Examples 28, 161, 162, 163, 165, 254, 255, 256, 269, 273, 274, 276, 277, 278, 280, 291, 292, 293, 493, 495, 506, 507, 510, 511, 525, 526, and 599.

16. The most relevant prior art is taught by Sakae et al. (US 6,136,823 A, 10/24/2000) where 1,4-dihydroquinolones were claimed that comprised instant formula (I) $-NR^{11}R^{12}$ as a primary amine or secondary lower alkyl amine. The entire series of quinolones taught by Sakae et al. contain quinolone nitrogens substituted with optionally substituted phenyl and pyridyl groups. Other related prior art has been taught by Wityak et al.(US 6,130,231 A,10/10/2000; US 6,358,976 B1, 3/19/2002) and Miyake et al. (US 5,889,009 A, 3/30/1999). These references taught heterocyclic, alkyl-heterocyclic, and alkyl-aryl substitution at the 7-position of the quinolone ring system. Losasso et al. (J. Chemother. Oct. 1995, 7(5), 420-423) teach away from the the use of two related and specific quinolones as platelet aggregation inhibiting agents.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David E. Gallis whose telephone number is 571-272-9068. The examiner can normally be reached on Mon-Fri 7:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-1600. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

David E. Gallis
Patent Examiner

JANET L. ANDRES
SUPERVISORY PATENT EXAMINER

I assume this was on my chair because you wanted me to review it?

done ✓ ▪ Box 4 on the 326: include all pending claims as pending.

done ✓ ▪ I'd object to all of the claims that encompass non-elected subject matter, including those otherwise rejected.

done ✓ ▪ Claim 15 should be "A" pharmaceutical composition. No antecedent basis for "the", since none of the claims from which it depends recite a pharmaceutical composition.

defined ✓ the enabled compound and cited the examples in the disclosure (see #6 & #15 also new reference at end of rejection) ▪ Enablement rejection: Applicant states that the compounds inhibit platelet aggregation by inhibiting P2Y12, so, at least according to Applicant, showing that a compound inhibits P2Y12 is the equivalent of showing that it inhibits platelet aggregation. A quick PubMed search indicates that Applicant is probably correct - that's how the leading platelet aggregation inhibitor works. So I'd accept that assertion and assume that inhibition of P2Y12 is equivalent to inhibition of platelet aggregation. Then decide what scope of the elected compounds is enabled. We generally give them more breadth than a single compound. Can you describe closely related compounds that would be expected to have similar activity? Point 5 of your rejection is actually the strongest point. They have shown us one compound within the elected scope that has activity. There is no guidance as to what other molecules that have been elected would have similar activity: Applicant provides no guidance as to what parts of the molecule are essential for its activity and what moieties could be altered without affecting this activity. The prior art fails to provide compensatory teaching, since compounds with this structure are known as antimicrobials. Thus, without further guidance as to the structural requirements for activity, the artisan would not be able to predict which molecules within the scope of the claims would be useful as platelet aggregation inhibitors, and it would require undue experimentation to practice the invention as broadly claimed.

all claims now include (see #5) ▪ No enablement rejection has been applied to the claims that recite no intended use. The compounds do have to have A use, and the only disclosed use that I see in the specification is the intended use of inhibition of platelet aggregation. So if there is no other disclosed use for the compounds, all of the claims should be rejected under 112 1st. In addition, pharmaceutical compositions, as in claims 15-17, must have a pharmaceutical use, so these claims have the same considerations as claims 1 and 2.